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| EXAMINER | |
|---|---|
| JEAN-LOUIS, SAMIRA JM | |

| ART UNIT | PAPER NUMBER |
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| 1617 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/560,669 | COUTRE, STEVEN | |
| | Examiner | Art Unit | |
| | SAMIRA JEAN-LOUIS | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *05 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-19* is/are pending in the application.

4a) Of the above claim(s) *1,2,4-7,10 and 17-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3, 8-9, and 11-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *04/19/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/Restrictions*

Claims 1-19 are currently pending in the application.

Applicant's election of Group II (i.e. method of treatment) and election of midostaurin as the elected species of staurosporine derivative in the reply filed on 03/05/09 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Thus, the requirement is deemed proper and is therefore made FINAL.

Claims 1-2, 4-7, 10, and 17-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected group and species, there being no allowable generic or linking claim. Claims 3, 8-9, and 11-16 are examined on the merits herein.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 9 and 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention (**see M.P.E.P 608.01 (k)**).

Claim 9 is particularly vague as applicant is claiming a compound, omatinib which is not known while claims 14-16 recite both a broad and a narrower dosage range using the word preferably (**in sentence 3 of claims 14-16**). Given that the compound omatinib is not known and applicant's recitation of the term "preferably" does not discern particular boundaries of the claims, one of ordinary skill in the art would not be able to fully ascertain the metes and bounds of the aforementioned claims.

As a result of the above inconsistencies, the aforementioned claims are unable to be examined as disclosed given that the scope of the claimed subject matter would not be able to be determined by one of ordinary skill in the art. However, for the sake of compact prosecution, the Examiner will construe that the stated species set forth in claim 9 is "Imatinib", a compound well-known to be resistant to mastocytosis and that the dosage range of formula VII varies from 100-300 mg.

***Claim Rejections - 35 USC § 101***

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 3, 8-9 and 14-16 provide for the use of a staurosporine derivative, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it

merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 3 , 8-9 and 14-16 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3, 8-9, and 14-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3, 8-9, and 14-16 are particularly vague as applicant is claiming a use without any active, positive steps delimiting how this use is actually practiced. Given that such claims recites a process without setting forth any steps, one of ordinary skill in the art would not be able to fully ascertain the metes and bounds of the aforementioned claims.

As a result of the above inconsistencies, the aforementioned claims are unable to be examined as disclosed given that the scope of the claimed subject matter would not be able to be determined by one of ordinary skill in the art.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3, 8-9, and 13-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the treatment of mastocytosis, does not reasonably provide enablement for the use of a staurosporine derivative for the preparation of a pharmaceutical composition for the curative, palliative, or prophylactic treatment of mastocytosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to the use of a staurosporine derivative or a salt thereof, if at least one salt-forming group is present for the preparation of a pharmaceutical composition for the curative, palliative, or prophylactic treatment of mastocytosis. The instant specification fails to provide information that would allow the

skilled artisan to practice the cure or prevention of mastocytosis with the staurosporine derivative of formula I.

Attention is directed to *In reWands,* 8USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman,* 230 USPQ 546 (BdApls1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to the use of a staurosporine derivative or a salt thereof, if at least one salt-forming group is present for the preparation of a pharmaceutical composition for the curative, palliative, or prophylactic treatment of mastocytosis. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites the fact that Longley et al. (cited by applicant and filed on an IDS 1449) teaches that no cure for mastocytosis exists yet applicant claims the cure and prevention of mastocytosis and provides no adequate support for such recitation.

2. The breadth of the claims

Since the instant specification provides no limiting definition of the term "prophylactic", the examiner will adopt the broadest reasonable interpretation for same. Webster's Ninth New Collegiate Dictionary defines "prophylactic treatment" as "prevention", i.e., to keep from happening.

The claims are thus very broad insofar as they recite the use of a staurosporine derivative or a salt thereof, if at least one salt-forming group is present for the preparation of a pharmaceutical composition for the curative, palliative, or prophylactic treatment of mastocytosis, yet applicant only provides enablement for decreasing and reduction of mast cells and no prevention of mastocytosis as previously stated.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for the use of a staurosporine derivative or a salt thereof, for the curative or prophylactic treatment of mastocytosis. In fact, applicant only provided guidance for reduction of circulating mast cells and inhibition of the receptor tyrosine kinase KIT using 1.0 and 10 μM dose of PKC412 or midostaurin. No reasonably specific guidance is provided concerning useful curative or preventive protocols for mastocytosis, other than examples 3-4 and 6. The latter is corroborated by the working examples on pages 44-45 and 48.

As a result, countless experimentation would be necessary to determine if in fact the

staurosporine derivatives of formula I can in fact cure or prevent mastocytosis as claimed by applicant.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed staurosporine derivatives could be predictably used to cure and prevent mastocytosis as inferred by the claims and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the invention claimed in the patent a person of ordinary skill in the art would have to engage in undue experimentation in order to determine if the staurosporine derivatives can indeed cure or prevent mastocytosis, with no assurance of success.

Genentech, 108 F.3d at 1366 states that " a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, the use of a staurosporine derivative or a salt thereof, if at least one salt-forming group is present for the preparation of a pharmaceutical composition for the curative, palliative, or prophylactic treatment of mastocytosis is not considered to be enabled by the instant specification. The claims are being examined herein for a

method of treating mastocytosis comprising a staurosporine derivative of formula I or formula VII.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Claims 3, 8, and 11 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Longley et al. (Hematology/Oncology Clinics of North America,, Vol. 14, No. 3, pgs. 689-695, cited by Applicant and filed on an IDS 1449) in view of Goekjian et al. (Experts Opinions on Investigational Drugs, December 2001, Vol. 10, No. 12, pgs. 2117-2140, previously submitted).**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Longley et al. teach that the treatment of mastocytosis is designed to prevent or ameliorate the deleterious effects of mast cell mediators rather than to eliminate the mast cells which produce and release them (see pg. 689). Longley et al. further teach that current forms of therapy while they lead to a decrease of mast cell numbers also cause significant adverse side effects (see pg. 690, paragraph 2). However, recent studies have suggested that mutations affecting the protein coding region of the c-kit proto-oncogene may cause some forms of mastocytosis (see pg. 690, paragraph 3). C-kit encodes a receptor tyrosine kinase whose cognate ligand is mast cell growth factor. Activation of mast cell growth factor receptor or kit stimulates mast cell growth and prevents apoptosis. Furthermore, activating mutations have been found as somatic mutations in the neoplastic mast cells of patients with mastocytosis. Thus, the consistent finding of activating c-kit mutations in mast cell tumors, together with the ability of activated kit to stimulate mast cell proliferation and transformation, suggests that these mutations are necessary if not sufficient, for some forms of mastocytosis (see pg. 690, last paragraph). Moreover, Longley et al. teach that inhibiting activating kit with kit inhibitors might be therapeutically useful in mastocytosis, might provide symptoms relief, decrease mast cell load and might eventually provide a cure by completely eliminating the neoplastic mast cell clone (see pg. 690, last paragraph). Additionally,

Longley et al. demonstrated that kit kinase inhibitors can effectively kill neoplastic mast cells which cause some forms of mastocytosis (see pg. 693, last paragraph).

Longley et al. do not specifically teach midostaurin or PKC412 as the kit kinase inhibitor effective in treating mastocytosis.

Goekjian et al. teach midostaurin or PKC-412 as an inhibitor of PKC that effectively inhibit signal transduction pathways (see pg. 2117, abstract). Goekjian et al. also teach that first generation staurosporine analogues CGP41251 or PKC-412 or midostaurin achieves a greater level of kinase selectivity and potential therapeutic index as a PKC inhibitor and tends to be non-toxic in light of mixed kinase inhibition that it exhibits (see pg. 2123. right col., last paragraph). Importantly, Goekjian et al. teach that midostaurin is a broad range kinase inhibitor and has been found to inhibit the stem cell factor receptor c-kit (i.e. midostaurin is a kit inhibitor; see pg. 2124, table 1 and Section 3.1).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the midostaurin of Goekjian et al. for the treatment of mastocytosis since Goekjian et al. teach midostaurin as a non-toxic kit inhibitor and Longley et al. teach that mastocytosis can be best treated with kit inhibitors. Thus, given the teachings of Longley and Goekjian, one of ordinary skill would have been motivated to utilize midostaurin in light of the disclosures of Goekjian and Longley with

the reasonable expectation of providing a method effective in treating mastocytosis with a low toxicity staurosporine derivative.

**Claims 9 and 12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Longley et al. (Hematology/Oncology Clinics of North America,, Vol. 14, No. 3, pgs. 689-695, cited by Applicant and filed on an IDS 1449) in view of Goekjian et al. (Experts Opinions on Investigational Drugs, December 2001, Vol. 10, No. 12, pgs. 2117-2140, previously submitted) as applied to claims 3, 8, and 11 above and in further view of Ma et al. (Blood, 2002, Vol. 99, No. 5, pgs. 1741-1744).**

The Goekjian and Longley references are as discussed above and incorporated by reference herein. However, Goekjian and Longley do not teach treatment of mastocytosis resistant to imatinib.

Ma et al., however, teach that adult-type or sporadic adult-type human mastocytosis (SAHM) is characterized by mutations in c-kit codon 816, which causes constitutive activation of the KIT kinase (see pg. 1741, left col. paragraph 1). Ma et al. also teach that mast cell lines and canine mast cell tumors also express activating c-kit mutations and small molecules that inhibit mutant activated KIT was able to effectively kill these cell lines (see pg. 1741, left col., paragraph 1). Ma et al. further teach that STI571 (i.e. imatinib) while effectively in inhibiting regulatory mutations or RT mutations did not significantly inhibit enzymatic site or EST mutations associated with SAHM (see

abstract, pg. 1741). Importantly, Ma et al. demonstrated that mast cell lines with EST mutations was not inhibited by STI571 suggesting that certain kit inhibitors such as STI571 is effective against certain mastocytosis and not SAHM (see abstract pg. 1741). Moreover, Ma et al. teach that these results suggest that mutations that are either classify as RT or EST may be useful in predicting tumor sensitivity or resistance to inhibitory drugs (see abstract, pg. 1741 and pg. 1743, right col.). This suggests that certain mastocytosis is resistant to imatinib.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to try the midostaurin of Longley in sporadic adult-type mastocytosis since Goekjian teaches that midostaurin is a potent inhibitor of c-kit with low toxicity. Given the teachings of Longley, Goekjian, and Ma, one of ordinary skill would have been motivated to try midostaurin in light of the disclosures of Goekjian, Longley, and Ma with the reasonable expectation of providing a method effective in treating sporadic adult type mastocytosis with a potent and low toxicity staurosporine derivative.

**Claims 13-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Longley et al. (Hematology/Oncology Clinics of North America,, Vol. 14, No. 3, pgs. 689-695, cited by Applicant and filed on an IDS 1449) in view of Goekjian et al. (Experts Opinions on Investigational Drugs, December 2001, Vol. 10, No. 12, pgs. 2117-2140, previously submitted) as applied to claims 3, 8, and 11 above and in further view of Caravatti et al. (U.S. 5,093,330).**

The Goekjian and Longley references are as discussed above and incorporated by reference herein. However, Goekjian and Longley do not teach the exact dosage of midostaurin to be used in the treatment of mastocytosis or the method of administration.

Caravatti et al. teach N-substituted derivatives of staurosporine including N-benzoyl-staurosporine (see abstract and col. 28, lines 45-57). Caravatti et al. further teach that the aforementioned active ingredients can be administered in an effective amount in a daily dosage from 1 to 1000 mg depending on the species, body weight, age, individual conditions, desired method of administration and the type of disease (see col. 23, lines 3-29). As for the mode of administration, the Examiner contends that it would be well within the purview of the skilled artisan to administer midostaurin at least daily for at least one week, discontinue the treatment if patient improves, and subsequently restarting treatment as desired during the course of experimentation depending on the desired treatment as taught by Caravatti et al.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to vary the mode of administration and treat mastocytosis in the range of 1 to 1000 mg since Caravatti et al. teach that one of ordinary skill in the art can vary the concentration depending on the desired mode of administration, disease, and the patient to be treated. Thus, given the teachings of Goekjian, Longley and Caravatti et al., one of ordinary skill would have been motivated to utilize midostaurin and vary the dosage and mode of administration in light of the disclosures of Goekjian, Longley, and

Caravatti with the reasonable expectation of providing a method effective in treating mastocytosis with a potent and low toxicity staurosporine derivative.

**Conclusion**

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1617

05/06/2009

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1617